REMARKS

Claims 31, 32, 71, and 75-91 were pending in the instant application. By this amendment, claims 32 and 75 have been cancelled without prejudice to the applicants' right to pursue the subject matter of the canceled claims in other applications. In addition, to clarify the invention, claims 31, 71, and 86-91 have been amended and claims 92 and 93 have been added. In particular, claim 31 has been amended to replace "decreases" with "interferes with." Support for the amendment is found at page 49, lines 24-26 and page 30, lines 25 and 26. Claim 71 has been amended to replace "modulating" with "inhibiting." Support for this amendment is found at page 26, lines 25-28. Claims 86, 87, and 88 have also been amended to delete dependency on claim 71. In addition, claims 31 and 71 have been amended to clarify the negative limitation by re-ordering the ligands, claim 91 has been amended to recite "autoimmune antigen" in order to correct antecedent basis, and claims 89, 90, and 91 have been amended to an alternative format rather than a Markush group. Support for claims 92 and 93 is found at page 23, lines 10-14. Thus, no new matter has been added.

Therefore, claims 31, 71, and 76-92 are pending in the instant application. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claims 31-32, 71, and 75-91 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner contends:

> The removal of a species from the claim under *In re Johnson* if and only there is support in the specification for the removal of

> the species. In this case, there is no support in the specification for a negative limitation so as to exclude an HSP, a complex of an HSP and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2) macroglobulin and a peptide.

The Examiner's rejection is based on the premise that the removal of a species from a claim under *In re Johnson* is appropriate if and only if there is support in the specification for the removal of the species. The Examiner further argues that *Johnson* requires support in the specification for a negative limitation so as to exclude the undesired species.

Applicants respectfully disagree. In accord with *In re Johnson*, "a broad and complete generic disclosure, coupled with extensive examples" constitutes support for removal of species. *In re Johnson*, 194 U.S.P.Q. 187, 196 (C.C.P.A. 1977). In *Johnson*, a genus of polyarylene polyethers, referred to as E′ precursor compounds, is disclosed together with examples that detail numerous species of polyarylene polyethers. "[This] broad *class* [the E′ genus] is identified as embracing suitable *choices* for the E′ precursor compound." Appellants in *Johnson* amended the claims to recite a proviso that removed two of the species, forming a "limited genus." In relation to rejections under § 102 or § 103 (which raised issues under §§ 112 and 120), of the claims containing the proviso, the court held that the "specification supported the claims *in the absence of the limitation*, and that specification, having described the whole, necessarily described the part remaining." [*Emphasis added*] *Id.* at 197.

Thus, according to the *Johnson* standard, in the present case support for removal of one or more species of alpha (2) macroglobulin ligands from a claim would require a complete generic disclosure of alpha (2) macroglobulin ligands, coupled with an extensive list of examples of alpha (2) macroglobulin ligands. Contrary to the Examiner's contention, the specification need not contain a negative limitation so as to exclude an HSP, a complex of an HSP and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2)

macroglobulin and a peptide.

Applicants assert that there is sufficient support for removal of one or more species of alpha (2) macroglobulin ligands from a claims 31 and 71. The specification provides a broad and complete generic disclosure of alpha (2) macroglobulin ligands, as well as extensive examples of ligands of the alpha (2) macroglobulin receptor. The genus of alpha (2) macroglobulin receptor ligands is defined functionally as having the ability to bind to a binding domain of the alpha (2) macroglobulin receptor (See page 3, lines 21-27 of the specification, which teaches the binding domain). The specification discloses numerous species within the genus, such as lipoprotein complexes, lactoferrin, tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), and exotoxins, as well as HSPs and HSP peptide complexes, and alpha (2) macroglobulin (see page 12, lines 14-17; page 14, lines 23-25).

Thus, the specification contains a sufficiently broad and complete generic disclosure of alpha (2) macroglobulin ligands, as well as extensive examples of species of alpha (2) macroglobulin ligands to support the proviso in claim 31 and 71. According to *Johnson*, this constitutes sufficient support for the proviso excluding one or more species of alpha (2) macroglobulin ligands, *i.e.*, an HSP, a complex of an HSP and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2) macroglobulin and a peptide. As in *Johnson*, *ipsis verbis* support for the specific negative limitation is not required.

In view of applicable case law and the support provided in the specification, applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

2. THE OBJECTION UNDER 35 U.S.C. § 132 FOR INTRODUCTION OF NEW MATTER SHOULD BE WITHDRAWN

The amendment filed November 7, 2002 has been objected to under 35 U.S.C. § 132 because it allegedly introduces new matter into the disclosure. The Examiner alleges

that the exclusion of an HSP, a complex of an HSP and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2) macroglobulin and a peptide which is able to modulate the interaction of a first HSP with and alpha (2) macroglobulin receptor is not supported by the original disclosure.

In the present instance, the support for the limitation is analogous to the support that the court found acceptable in *Johnson* (see reasoning presented above in response to 35 U.S.C. § 112, first paragraph, rejection).

Applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 132.

3. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 32, 71, 78, 83, 84, and 85-91 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure. In particular, the Examiner contends that there is no enablement for administering a compound that is an agonist capable of enhancing the interaction of the HSP with alpha (2) macroglobulin receptor. The Examiner also contends that the disclosure of assays for measuring receptor activity alone is insufficient to enable the invention because a compound could increase binding affinity between two proteins and not necessarily increase receptor activity. The Examiner further contends that undue experimentation would therefore be required by one skilled in the art to discover or define a compound from a multitude of potential candidates.

In response, claims 32, 75, 78, 83, and 84 have been canceled and claim 71 has been amended to replace "modulating an immune response" with "inhibiting an immune response." Applicants submit that the rejection has been obviated by the amendment to the claims for the reasons set forth below.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent

specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); see also *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Based on the legal standard above, the specification clearly enables methods for inhibiting an immune response recited in claims 71 and 85-91, and newly added claims 92 and 93. The assays mentioned at page 35, lines 1-6, can be used to determine whether a

compound that binds to the alpha (2) macroglobulin receptor inhibits an immune response. Examples of assays include: assays for stimulation of cytotoxic T cells, disclosed at page 36, line 20 through page 37, line 2; antigen presentation assays, disclosed at page 32, lines 7 to 19; and the cytokine release assay, taught at page 35, lines 3 and 4. Thus, the assays taught in the specification clearly enable one skilled in the art to identify compounds that inhibit an immune response without engaging in undue experimentation.

With respect to the Examiner's contention that screening a multitude of potential candidate compounds would require undue experimentation, applicants respectfully disagree and point out that screening different types of compounds and large libraries thereof was routinely practiced in the pharmaceutical industry at the time of the effective filing date of the instant application. In support of this assertion, applicants invite the Examiner's attention to Houghten et al. (Houghten et al., 1991, Nature 354:84-86, hereinafter, "Houghten", submitted herewith as Exhibit A) and Kuhlmann (Kuhlmann, 1997, Int. J. Clin. Pharmacol. Ther. 35:541-552, submitted herewith as Exhibit A; hereinafter referred to "Kuhlmann"). Houghten teaches methods for synthesizing and screening recombinatory libraries of peptides, which allowed the skilled artisan to screen millions of compounds at a time. Kuhlmann is a review that reflects the state-of-the-art of high-throughput screening methods which made it possible for the skilled artisan at the time to readily screen and test large numbers of compounds. These references demonstrate that high throughput techniques for drug discovery routinely allowed identification and screening of a multitude of potential candidate compounds, and did not require undue experimentation.

Furthermore, testing the identified compounds *in vivo* for the ability to inhibit an immune response would also be routine to the skilled artisan in the industry. The specification teaches screening from entire libraries of compounds, see section 5.2.3, page 37, line 20 through page 40, line 8. The specification also teaches numerous *in vivo* testing methods, see page 29, lines 3-13. Thus, one skilled in the art would not need to engage in

undue experimentation to assay for and test compounds for use in the methods of the invention.

In view of the forgoing reasoning and amendments, applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

4. THE REJECTION UNDER 35 U.S.C. § 102, AS BEING ANTICIPATED BY PIZZO *ET AL.*

Claims 71, 76, 83, and 84 have been rejected under 35 U.S.C. § 102 as allegedly anticipated by Pizzo et al. The Examiner points out that Pizzo teaches compounds that decrease or increase alpha (2) macroglobulin receptor activity and are peptides, small molecules, or alpha (2) macroglobulin-peptide complexes. Applicants' previous argument that the removal of a species so as to render the claims unanticipated by the prior art is supported by *In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977) was not found persuasive. Applicants respectfully disagree.

In the present instance the support for the negative limitation is analogous to the support that the court found acceptable in *Johnson* (see reasoning presented above in response to 35 U.S.C. § 112, first paragraph, rejection). In view of applicable case law and the support provided in the specification, applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 102, over Pizzo.

5. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, FOR INDEFINITENESS SHOULD BE WITHDRAWN

Claims 31, 32, 71, and 75-91 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. First, the Examiner contends that the term "decrease" is relative and must be compared to a control level. With regard to the rejection of claim 31, the claim has been amended to replace "decreases" with

"interferes with." Thus, the rejection with respect to "decreases" has been obviated by the amendment to claim 31.

Secondly, the Examiner contends that the term "effective amount" is not clearly defined in the specification and that the amount administered to be effective is not clear. Finally, the Examiner contends that the term "modulate" is indefinite, since it is unclear how a decrease in the interaction of an HSP with an alpha (2) macroglobulin receptor would result in the modulation of an immune response.

The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). Thus, according to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985).

With respect to the rejection of claim 31 and dependent claims thereon based on the alleged indefiniteness of the term "amount effective," applicants submit that the term has a clear meaning when viewed in light of the specification as a whole. One skilled in the art would have a definite understanding of the term because methods for determining an amount effective to modulate an immune response are described in the specification and/or would be known to the skilled artisan. For example, Section 5.10.5 teaches dosage of compounds of the invention. A therapeutically effective dose is taught to vary, depending on the route of administration and form of the compound, and can be estimated based on cell and animal models. *In vitro* assays disclosed in the specification provide guidance for an effective amount to modulate an immune response. (See *e.g.*, the assays described at page 35, lines 7-26, and Section 6 at page 73, lines 1-9 and Figure 2B). One skilled in the art would undoubtedly look to such results for guidance in determining an amount effective *in*

vivo, which can then be optimized based on *in vivo* results. Thus, the term "amount effective to modulate an immune response" would be understood by one skilled in the art to be the amount necessary to effectuate an immune response. One skilled in the art would understand the effective amount can vary significantly depending on the particular human to which the methods of the invention are applied.

With respect to recitation of the term "modulate," the term has a clear and definite meaning when construed in light of the specification. The Examiner's attention is invited to page 30, lines 24-27 of the specification where "modulate" is described as "interfere with or enhance" in the context of screening assays. One skilled in the art would recognize that this meaning of "modulate" is the standard meaning and applicable to the use of the term throughout the specification. Thus, the meaning of the term "modulate" with respect to an immune response is not indefinite when construed in light of the specification.

Moreover, the Examiner has based the rejection upon an assertion that "it is unclear how a decrease in the interaction of an HSP with and an alpha (2) macroglobulin receptor would result in the modulation of an immune response." Applicants respectfully submit that this assertion is an improper basis for an indefiniteness rejection. There is no requirement that the mechanism through which the invention works be known. See Exxon Chemical Patents, Inc. v. Lubrizol Corp. 77 F.3d 450 at 456.

> An inventor need not understand the scientific mechanism in order to place an invention into the patent system. See Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed.Cir.1989) (observing that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"); Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed.Cir.1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

Thus, it is irrelevant how decreasing the interaction of an HSP with the alpha (2) macroglobulin receptor results in the modulation of an immune response - - it is only

important to know the desired outcome. The requirement for definiteness is whether one skilled in the art would understand what is claimed in light of the specification, which has been addressed above.

Nevertheless, the Examiner's attention is drawn to Section 6 of the specification where the applicant demonstrates that the alpha (2) macroglobulin receptor is the receptor for HSPs. Therein, HSPs are disclosed which are taught to chaperone peptides into a cell via the alpha (2) macroglobulin receptor and elicit an immune response (see page 71, lines 14-20, and page 72, lines 25-28). One skilled in the art would clearly recognize that interfering with the interaction of HSPs with an alpha (2) macroglobulin receptor would interfere with eliciting an immune response.

In view of the forgoing arguments and amendments, applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants respectfully request that the present remarks and amendments be entered and made of record in the instant application. It is submitted that the foregoing amendments and arguments made herein place the claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is believed that no fee is required for filing this amendment. In the event a fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

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